**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Dahm et al.

Serial No.: 09/601,645

Filed: August 4, 2000

For: METHOD FOR THE QUANTITATIVE DETERMINATION OF TUMOR CELLS IN A BODY FLUID AND TEST KITS SUITABLE THEREOF

Art Unit: 1655

Examiner: Zitomer, S.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner for Patents,
Washington, D.C. 20231, on this date.

12/26/01
Date

Stephanie L. Seidman

#14



**PETITION UNDER 37 C.F.R. §1.144**
**PETITION FROM REQUIREMENT FOR RESTRICTION**

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicant hereby petitions under 37 C.F.R. §1.144 from a Restriction Requirement in the above-captioned application. Applicant respectfully requests removal of the Requirement as between Groups I-III.

**STATEMENT OF FACTS**

The Requirement sets forth three groups as follows:

Claims in Group I are directed to methods for quantification of tumor cells in a body fluid by concentrating or depleting tumor cells in a sample of a body fluid; specifically amplifying mRNA coding for the catalytic subunit of telomerase; and then quantitatively determining the amount of amplified nucleic acid to thereby quantifying tumor cells in a body fluid. Dependent claims specify particulars of the method, including the primers.

Claims in Group II are directed to methods for quantification of tumor cells in a body fluid by concentrating or depleting tumor cells in a sample of a body fluid; specifically amplifying mRNA coding for the catalytic subunit of telomerase; and then quantitatively determining the amount of amplified nucleic

acid to thereby quantifying tumor cells in a body fluid. Claim 20 is directed to the method of claim 1 and specifies that the cells are concentrated by layering the body fluid onto a cell separation medium and centrifuging the layered fluid and medium. Dependent claims specify particulars, for example, regarding the cell separation medium. Hence group II is directed to the method of Group I, and specifies particulars of the method.

Claims in Group III are directed to specific primers and to a kit containing the primers. Dependent claims in Group I, specify that these primers are used for amplification.

The first Requirement was set forth in a written Restriction Requirement, mailed May 1, 2001. The Requirement set forth two (2) Groups for election. Applicant elected, with traverse, Group I in a paper mailed June 1, 2001. Receipt of the paper mailed June 1, 2001, was acknowledged. The original Requirement was, however, reconsidered, and a new Requirement was set forth in a written Restriction Requirement mailed July 3, 2001. The Requirement set forth three (3) Groups for election. Applicant elected, with traverse, Group II in a paper mailed August 3, 2001. Applicant's arguments were not deemed persuasive. The Requirement was made final in an Office Action, mailed October 24, 2001. Since the Office was officially closed on December 24, 2001 and December 26, 2001, this Petition is timely filed.

**PCT Rule 13**

This application is the U.S. national stage of International Patent Application No. PCT/EP99/00716, filed in accordance with 35 U.S.C. §371. Applicant notes that no lack of unity objection was raised during either Chapter I or II at the international stage.

As stated in MPEP 201, national stage applications of international applications are similar to national applications, but there are differences. Among these differences is inapplicability of restriction practice to national stage applications. Restriction practice is applied to national applications, but unity of

invention practice is applied to national stage applications (see, MPEP 201 and MPEP 1893.03(d)). Therefore, the applicable rule with respect to the instant national stage application is PCT Rule 13.1.

**Lack of Unity Standard**

When the U.S.Patent Office considers an international application during the national stage, restriction must be based on unity of invention, which is governed by PCT Rule 13 (see MPEP 1893.03(d); Caterpillar Tractor Co. v. Commissioner of Patents and Trademark, 650 F. Supp. 218, 31 USPQ 590 (E.D. Virginia, 1986); In re Caterpillar Tractor Co, 228 USPQ 77). In the Caterpillar cases it was ultimately held that the language in Rule 13.1 "specially adapted" is not to be interpreted as meaning that the process of manufacture can only be used to manufacture the product because this interpretation is in conflict with the PCT Rule, which provides that no national law shall require compliance with requirements relating to the form or contents of the international application different from or additional to those which are provided in the Treaty (Article 27 of the PCT). Thus, the U.S. Patent Office cannot impose requirements that differ from those provided in the Treaty. Since restriction practice differs from and is more restrictive than unity of invention, the unity of invention rules must govern.

Therefore, it is respectfully submitted, and it appears that the Office has acknowledged, that the rules of unity of invention (PCT Rule 13.1 and 37 C.F.R. §1.475) apply to this application. Rule 13.1 requires that an international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

This application was filed under 35 U.S.C. §371 and is the national stage of an international PCT application.

**ARGUMENT**

Applicant respectfully petitions for reconsideration and removal of the Requirement as between Groups I, II and III, and particularly as between Groups I and II, in view of the following remarks.

The Office Action, mailed October 24, 2001, urged that the Restriction Requirement is based on the allegation that the various Groups do not relate to a single inventive concept under PCT Rule 13.1 for unity of invention. This conclusion is based upon the Examiner maintaining the premise, despite Applicant's traversal that the single general inventive feature between the two groups is "mRNA encoding the catalytic subunit of human telomerase." The Examiner urges that this mRNA is known (Genbank) and also urges that the method for quantifying mRNA is known in the art (U.S. Patent No. 5,726,019). The Examiner also urges that Applicant's arguments are not persuasive because it is alleged that none of the Group I particulars of amplifying and quantifying mRNA are found in the Group II claims and conversely, the Group II methods for concentrating tumor cells from blood involving culture, centrifugation and cell separation medium are not found in the Group I claims. Consequently, the Examiner maintains that the mRNA for the catalytic subunit of telomerase is the special technical feature of Groups I and II.

Further, in the written Restriction Requirement mailed July 3, 2001, the Examiner alleged that the claimed method of amplifying mRNA from tumor cells in body fluid by measuring the amount of specific mRNA in the cells was practiced in the art as taught by Sidransky (U.S. Patent No. 5,726,019) and Selby (GB 2 260 811) and the claimed method of concentrating tumor cells was also taught by Selby. In the paper mailed August 3, 2001, Applicant argued that neither of the references taught or suggested anything about telomerase or mRNA coding for the catalytic subunit of telomerase. In response, in the Office Action mailed October 24, 2001, that set forth the finality of the Requirement the Examiner urges that these references were cited as a courtesy to Applicant

to show that concentrating cells and amplifying and quantifying mRNA were known techniques in the art, that the issue is restriction, not rejection over prior art, and that the Examiner was only required to provide a reference disclosing the special technical feature.

With regard to obviousness-type double patenting, the Examiner urges that claims of Group II are directed to a generic concentration method and the particulars of Group I would not be obvious over the generic method, unless each group of claims were amended to include particulars from the other, in which case obviousness-type double patenting would apply.

Applicant respectfully disagrees with the Examiner's characterization of the common inventive feature of the claims, for the reasons set forth below. Briefly, claims of Group II are dependent on claims of Group I, and, hence by virtue of the definition of dependent claims, Group II includes all of the particulars of group I. For example, claim 1 of Group I is as follows:

> A method for the quantification of tumor cells in a body fluid, comprising:
> (a) concentrating or depleting tumor cells in a sample of a body fluid; and
> (b) specifically amplifying mRNA coding for the catalytic subunit of telomerase; and
> (c) quantitatively determining the amount of amplified nucleic acid, thereby quantifying tumor cells in a body fluid.

Claim 20 of Group II is as follows:

> 20. The method of Claim 1, wherein for concentrating the tumor cells, a cell separation medium is covered with a layer of the body fluid and centrifuged.

Hence, claim 20 is directed to the method of claim 1 and specifies particulars of step a). If claim 1 is deemed allowable, claim 20, which includes all limitations thereof must also be deemed allowable.

**Traverse of finding of lack of unity**

The Examiner, recognizing that the rules of unity of invention under PCT Rule 13.1 apply to the instant case, urges that there is a lack of unity because

the two groups do not relate to a single inventive concept. This conclusion is based upon the premise that the single general inventive feature between the two group is "mRNA encoding the catalytic subunit of human telomerase." The Examiner urges that this mRNA is known (Genbank) and also urges that the method for quantifying mRNA is known in the art (U.S. Patent No. 5,726,019). Applicant respectfully disagrees.

Claims in Group I are directed to methods for quantification of tumor cells in a body fluid by concentrating or depleting tumor cells in a sample of a body fluid; specifically amplifying mRNA coding for the catalytic subunit of telomerase; and then quantitatively determining the amount of amplified nucleic acid to thereby quantifying tumor cells in a body fluid. Dependent claims specify particulars of the method, including the primers.

Claims in Group II are directed to methods for quantification of tumor cells in a body fluid by concentrating or depleting tumor cells in a sample of a body fluid; specifically amplifying mRNA coding for the catalytic subunit of telomerase; and then quantitatively determining the amount of amplified nucleic acid to thereby quantifying tumor cells in a body fluid. Claim 20 is directed to the method of claim 1 and specifies that the cells are concentrated by layering the body fluid onto a cell separation medium and centrifuging the layered fluid and medium. Dependent claims specify particulars, for example, regarding the cell separation medium. Hence Group II is directed to the method of Group I, and specifies particulars of the method. It is not directed to a method for concentrating tumor cells nor to an apparatus. Group II is directed to a method for quantification of tumor cells. Claim 1 specifies that the tumor cells are concentrated and Group II includes some specifics about the step of concentrating.

Claims in Group III are directed to specific primers and to a kit containing the primers. Dependent claims in Group I, specify that these primers are used for amplification.

**Cited art**

**U.S. Patent No. 5,726,019**

This patent describes a method for diagnosing lung neoplasia and is based upon the discovery that a nucleic acid molecule that has as particular mutation is associated with lung neoplasia and that this nucleic acid molecule is present in detectable levels in sputum specimens from patients with lung neoplasia. U.S. Patent No. 5,726,019 does not teach or suggest that the amount of mRNA encoding a catalytic subunit telomerase can be used to quantify tumor cells in a body fluid. U.S. Patent No. 5,726,019 does not teach or suggest anything regarding telomerase or mRNA coding for the catalytic subunit of telomerase.

Therefore it does not anticipate any of the pending claims.

**Genbank submission**

The Examiner states that the sequence of cDNA from mRNA encoding the catalytic subunit of telomerase is available from Genbank. Even assuming that such sequence is known, the disclosure thereof provides no teaching suggestion that the amount of mRNA present in a body fluid can be used to quantitate tumor cells. Furthermore, the Genbank submission does not teach or suggest the particular primers used in the instant methods or kits.

Therefore it does not anticipate any of the pending claims.

**Selby (GB 2 260 811)**

Selby is directed to methods for diagnosing malignant tumors in which **total** mRNA is extracted from a sample of body fluid and reverse transcribed into cDNA, which is amplified using **primers** based upon **a tissue-specific gene not normally expressed in the body fluid**, followed by analysis to determine whether such amplified cDNA is present. Selby does not suggest using a gene for amplification that is not tissue specific nor does Selby suggest quantification of tumor cells in a body fluid. Selby, thus teaches using a tissue-specific gene, not a gene that is ubiquitously expressed.

Selby does not suggest using a gene for amplification that is not tissue specific nor does Selby suggest quantification of tumor cells in a body fluid. Selby does not suggest anything about the catalytic subunit of telomerase nor suggest that it can be used for quantification of tumor cells in a sample of body fluid. Selby does not teach or suggest that the amount of the mRNA encoding the catalytic subunit of telomerase can be detected in a body fluid nor that such a amount is related to the number of tumor cells in the fluid. Therefore it does not anticipate any of the pending claims.

Thus, the instant claims are clearly novel and are not taught or suggested by the combination of teachings of the cited references. Furthermore, the instant application teaches that the quantity of mRNA that encodes the catalytic subunit of telomerase correlates with telomerase activity better than the quantity of the RNA component of telomerase (International PCT application No. 97/18322; see, U.S. application Serial No. 09/068,821). Furthermore, neither reference, singly or in combination teaches or suggests the instantly claimed primers, used in the method and specified in dependent claims, and kits.

Therefore, the claims of Groups I and II do not lack unity and are so linked as to form a single inventive concept *i.e.* a method for quantifying tumor cells in a body fluid and primers used in the method. Accordingly, withdrawal of the lack of unity objection and restriction requirement is respectfully requested.

Furthermore, if the claims are divided into these groups, particular groups I and II, applicant ultimately could be granted two patents, one directed to the method for quantifying tumor cells in a body fluid by concentrating or depleting tumor cells in a sample of a body fluid; specifically amplifying mRNA coding for the catalytic subunit of telomerase; and then quantitatively determining the amount of amplified nucleic acid to thereby quantifying tumor cells in a body fluid, and a second patent directed to the same method, but specifying that the cells are concentrated by layering the body fluid onto a cell separation medium

and centrifuging the layered fluid and medium. If the second patent, which is directed to claims that are encompassed within the claims the first patent, were to issue first obviousness-type double patenting **could not** be held. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Therefore, withdrawal of the requirement for restriction as between Groups I-III, and most particularly, as between Groups I and II, is respectfully requested.

**Group III**

Group III is directed to primers and a kit containing the primers that are used in the amplification methods of Groups I and II. It is respectfully submitted that under the standard set forth in PCT Rule 13.1 the primers designed for use in the methods of Groups I and II relate to a single inventive concept and therefore should be examined in the same case as Groups I and II as it was in the international phase of examination.

**Summary**

Applicant petitions for removal of the Restriction Requirement as between Groups I, II and II, in particular between Groups I and II.

It is respectfully submitted that the Restriction Requirement as between Groups I and II is improper because the Group II claims are dependent on the Group I claims, and specify particulars of the Group I method, for example, regarding the cell separation medium and the particulars for tumor cell concentration. The Office must not restrict such Groups because if the claims to the dependent Group II claims that are encompassed within the Group I claims and further specify the particulars of concentration of the tumor cells issue first, then claims to the broader Group I claims cannot be held to constitute obviousness-type double patenting over an earlier issuing patent directed to the Group II claims.

Furthermore, the basis for the Examiner's assertion that there is a lack of unity is incorrect; the claims of Group I do not lack novelty over any of the cited references.

Therefore, Applicant respectfully requests reconsideration of the Restriction Requirement and that Groups I, II and III, or, alternatively, Groups I and II, should be combined for examination in the instant application.

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Respectfully submitted,
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